REMARKS

The Office Action mailed 9 March 2004 has been received and reviewed. Claims 58-75, 79, 80, 84, 85, 89-91, 95-7, 101 and 102 having been amended, and claim 103 having been added, the pending claims are claims 58-103. Reconsideration and withdrawal of the rejections are respectfully requested.

The recitation in claims 58, 62, 64, 66, 69 and 103 of an "ephrin comprising the extracellular domain of ephrinA1" is supported by the specification at, for example, page 3 lines 2-3 (". . .EphrinA1-Fc, the extracellular domain of ephrinA1 linked to immunoglobulin heavy chain..."); and page 7, lines 22-23 ("An example of another way to target EphA2 is the use of ephrins to activate or inhibit EphA2."). In this regard please also note the art-recognized nomenclature rules for the Eph family of receptors. Eph Nomenclature Committee, "Unified nomenclature for Eph family receptors and their ligands, the ephrins," Cell, 1997, Aug 8;90(3):403-4 (previously submitted).

The claims have been amended to delete recitation of the term "metastatic". In its place the amended claims now recite the generic terms "tumor" or "cancer". It is submitted that this amendment does not narrow the scope of the claims.

The recitation in claims 58 and 72 of "tumor volume" is supported by the specification at, for example, page 7, lines 29-30 (". . .[t]herapeutic amounts . . . eliminate or reduce the patient's tumor burden. . ."); page 13, lines 1-2 (". . .blocking the growth of primary prostate tumors. . ."); and Example 7 (page 16, line 16 bridging to page 17, line 34, including Table I.

New claim 103 is supported by the specification at, for example, page 3 lines 2-3 (". . .EphrinA1-Fc, the extracellular domain of ephrinA1 linked to immunoglobulin heavy chain...").

Examiner Interview Summary

The Examiner is thanked for the telephone interviews conducted May 27, 2004, and June 17, 2004, as described in the Interview Summaries mailed June 1, 2004, and June 18, 2004, respectively. All pending claims were discussed. The participants discussed the application of

the "written description" requirement under 35 U.S.C. §112, first paragraph to the use of the term "compound" in the claims, and the relevance of University of Rochester v. G.D. Searle & Co., Inc., Monsanto Company, Pharmacia Corporation and Pfizer Inc. (CAFC, 03-1304, decided February 13, 2004) in this regard as well. Applicants present herein arguments directed to this discussion.

Correction of Inventorship

A Request for Correction of Inventorship pursuant to 37 CFR 1.48(b) was submitted 13 February 2003. In the Office Action mailed 23 May 2003 the Examiner indicated that the request would be processed, but Applicants have received no subsequent indication that the request was granted. Applicants respectfully request that in the next Official Communication the Examiner indicate whether the Request for Correction of Inventorship has been granted.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner maintains the rejection of claims 58-71, 101 and 102 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

Claims 58-71, 101 and 102 were drawn to methods that involve the use of "a compound that increases the phosphotyrosine content of EphA2." The Examiner asserts that to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The Examiner asserts that, of the factors to be considered in evaluating the sufficiency of the written description of the genus "a compound," "the only factor present in the claim is a function." The Examiner acknowledges that the specification discloses that the ligand (EphrinA1) and an anti-EphA2 antibody have the recited function. However, the rejection is maintained because anti-EphA2 antibodies and the ligand do not share a common core structure so as to be representative of a genus called "compound". University of Rochester vs. G.D. Searle & Co, Inc., et al. (69 U.S.P.Q. 2d 1886, CAPC 2004) was cited by the Examiner as teaching that "how to screen" a

compound does not satisfy the written description requirement. The Examiner states that there is not, in the instant application, any identification of any common structure that has the recited function, and consequently, in the absence of "sufficient recitation of distinguishing identifying characteristics", the specification does not provide adequate written description of the claimed genus.

Applicants disagree with the Examiner's finding of a lack of written description, and maintain that in the present application, a "sufficient recitation of distinguishing identifying characteristics" has been supplied for at least the reasons detailed in the response filed November 24, 2003. In addition, the present matter is clearly distinguishable from the factual situation described in University of Rochester vs. G.D. Searle & Co, Inc., et al. (Rochester). In Rochester, claim 1 was directed to a method for selectively inhibiting COX-2 activity (as distinct form COX-1 activity) by administering a non-steroidal compound that selectively inhibits the activity of the PGHS-2 gene product. *Not one compound* had been identified that had the activity recited in the claims; the Rochester patent did not disclosure the structure or physical properties of any of the compounds required to practice the claimed methods, and the structure of such compounds cannot be deduced form any known structure function correlation. There was only a "hoped for function of an as-yet-to-be-discovered compound, and a research plan trying the find it." In addition, Rochester did not present any evidence that one of skill in the art would be able to identify any compound based on the function description "a non-steroidal compound that *selectively* inhibits activity of the COX2 gene product" (emphasis added). Although the University of Rochester scientists had developed a screening assay for use in determining whether a particular drug displayed such selectivity, it apparently was not demonstrated selectivity could even be achieved.

The present specification is significantly different in that it demonstrates, in working examples, at least two therapeutically effective compounds (EphrinA1-Fc and antibody B2D6, when aggregated). In addition, Applicants' own work since the filing of the application shows that additional compounds (namely, antibodies EA2 and B233) were identified using the methods taught in the specification (see Declaration of Michael S. Kinch under 37 C.F.R. §

1.132, submitted November 24, 2003). The record also shows that the methods set forth in the present application were successfully followed by other researchers (Koolpe et al., J. Biol. Chem. 277:49, 46974-46979, 2002) to identify other compounds that agonize EphA2. The Pasquale laboratory "exploited" (their own words) EphA2 as a therapeutic target to identify a peptide that agonizes EphA2, thereby taking advantage of the Applicants' contribution to the art, which they cited.

It is respectfully submitted that in elucidating the heretofore *unrecognized relationship* between activation of the EphA2 receptor and a therapeutic effect, and in providing two independent working examples (one involving an antibody, the other a peptide-ligand conjugate), Applicants have provided a *clear and direct path* for identification other compounds that exhibit this activity. Identification of such compounds requires at most only routine experimentation in light of the detailed teachings of the specification. It would be unjust to allow others to simply screen compounds for this activity without falling within the scope of the claims prior to amendment.

However, and notwithstanding the above arguments, the claims have been amended to advance prosecution of the instant application. In particular, recitation of the term "compound" has been deleted from independent claims 58, 62, 64, 66 and 69. In its place, these claims now recite an "an ephrin comprising the extracellular domain of ephrinA1." New claim 103, which depends from claims 58, 62, 64, 66 and 69, is directed to a method wherein the ephrin comprises ephrinA1-Fc. The Examiner is requested to note for the record that Applicants nonetheless continue to maintain that the specification provides sufficient distinguishing identifying characteristics of the genus of "a compound that increases the phosphotyrosine content of EphA2," for at least the reasons already made of record.

Applicants respectfully request reconsideration and withdrawal of the "written description" rejection of claims 58-71, 101 and 102 under 35 U.S.C. §112, first paragraph.

Claims 58-102 remain rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the claims containing subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it s most nearly connected, to make and/or use the invention. The Examiner notes that this rejection has several aspects. Applicants respectfully traverse the rejection.

The Examiner indicates that first, the rejection is made because claims 58-102 are interpreted as drawn to a method of reducing tumor metastasis. The Examiner states that neither the specification nor the data filed during the prosecution of the instant application has shown that the claimed method is effective for reducing metastasis. The Examiner suggested that amending the claim preambles to recite "method of treating and/or amending the effective of active steps to "reduce tumor volume" would obviate this part of the rejection.

To advance prosecution, the claims have been amended to delete references to metastasis and metastatic cells. Claims 58 and 73 have been further amended to recite a reduction in tumor volume. However, Applicants continue to maintain that the specification also enables a method of reducing metastasis.

The Examiner further indicates that, second, claims 58-71 and 101 are drawn to a method of treating a patient having a metastatic tumor with "a compound that increases the phosphotyrosine content of EphA2" which would require undue experimentation. The Examiner indicated that limiting the scope of the claims to a compound with common structure to EphrinA1 and/or anti-EphA2 antibody with the recited function would obviate the rejection.

To advance prosecution of the instant application, the claims have been amended. In particular, claims 58-71 and 101 have been amended to delete any reference to a "compound" and insert therefor "an ephrin comprising the extracellular domain of ephrinA1". New claim 103, which depends from claims 58, 62, 64, 66 and 69, is directed to a method wherein the ephrin comprises ephrinA1-Fc.

However, Applicants continue to maintain that the skill in the art is very high and that the assay for EphA2 phosphotyrosine content has been fully described in the specification, thereby enabling claims 58-71 and 101. Given the teachings of the specification and the skill level in the

art, Applicants assert that commonality of structure is not necessary in order for one of skill in the art to make and identify compounds that render the claimed methods operative, without undue experimentation.

Reconsideration and withdrawal of the rejection of claims 58-102 under 35 U.S.C. §112, first paragraph, is accordingly requested.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner newly rejected claims 62-65, 69-71, 79-88, and 95-102 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

The Examiner asserted that claims 62-65, 79-88, 101 and 102 are incomplete in that they omit a step that accomplishes the purpose stated in the preamble of the claims.

Independent claims 62 and 79, which recite in the preamble a method for treatment of a patient having a *tumor*, are amended to recite that the administration of the ephrin (claim 62) or the anti-EphA2 antibody (claim 79) impedes proliferation of the *tumor cells*. Claims 63-65 depend from claim 62, and claims 80-83 depend from claim 79.

Independent claim 84, which recites a method for treatment of a patient having a *tumor*, is amended to recite that the administration of the anti-EphA2 antibody increases the phosphotyrosine content of EphA2 in said tumor cells as compared to untreated *tumor cells*. Claims 85-88 depend from claim 84.

Claim 101 has been amended such that it also depends from claims 62, 79 and 84, and claim 102 has been amended such that it does not depend from any of claims 62-65 or 79-88. It is believed that these amendments obviate the rejection.

The Examiner asserted that claims 62, 69, 79 and 95 are confusing because it is not clear whether the active steps will result in reduction in formation of metastases, or kill already metastasized tumor cells. All dependent claims are rejected because they depend on the rejected base claims.

As previously noted, the claims have been amended to delete the recitation of "metastasis" or "metastatic cells". It is believed that these amendments obviate the rejection.

Reconsideration and withdrawal of the rejection of claims 62-65, 69-71, 79-88, and 95-102 under 35 U.S.C. §112, second paragraph, is accordingly requested

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner newly rejected claims 58-102 under 35 U.S.C. §112, first paragraph, as being failing to comply with the written description requirement. The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor(s), at the time of application was filed, had possession of the claimed invention. This rejection is characterized by the Examiner as "new matter" rejection directed at the phrase "a compound that increases the compound that increases the phosphorylation[sic] content of EphAA2[sic]". This rejection is respectfully traversed.

The pending claims recite an ephrin comprising the extracellular domain of ephrinA1 (claims 58-71 and 101-103) or an anti-EphA2 antibody (claims 72-102) that "increases the phosphotyrosine content of EphA2". The phrase "increases the phosphotyrosine content of EphA2" was introduced into the claims in an Amendment mailed February 13, 2003. In evaluating an amendment to a claim, "[a] study of the entire application is often necessary to determine whether or not 'new matter' is involved." MPEP 2163.06. Applicants respectfully submit that a study of the application shows that the recitation of "increases the phosphotyrosine content of EphA2" in the claims is fully supported by the application as originally filed and does not introduce new matter.

The Examiner acknowledges that the specification describes that EphrinA1-Fc can be used to increase the "phosphorylation" (i.e., phosphotyrosine) content of EphA2 but alleges that the specification as originally filed does not have support for "a *compound* that increases the phosphorylation[sic] content of EphAA2[sic]" (emphasis added). Applicants disagree.

To begin with, the pending claims no longer recite a "compound" that increases the phosphotyrosine content of EphA2. As amended, the claims recite an ephrin comprising the extracellular domain of ephrinA1 (claims 58-71 and 101-103) or an anti-EphA2 antibody (claims 72-103). Thus, it is respectfully submitted that the claim amendments obviate the rejection.

However, if and to the extent the Examiner applies the rejection to the pending claims, the following comments are presented. The instant invention advances the art by showing that stimulating, i.e., agonizing or activating, an EphA2 receptor has a therapeutic, anti-cancer effect. *Stimulation* of the EphA2 receptor is indicated by an *increase in phosphotyrosine content* of the EphA2 receptor.

The specification at page 3, lines 1-8, links the *stimulating* activity of *agonists* to *increase in EphA2 phosphotyrosine content*:

> Another approach to cancer treatment is to use *agonists to stimulate expression. For example*, EphrinA1-F_c, the extracellular domain of ephrinA1 linked to immunoglobulin heavy chain, (see Miao, H., et al., EphA2 kinase associates with focal adhesion kinase and upon activation, inhibits integrin-mediated cell adhesion and migration, Nature Cell Biol 2, 62-69 (2000), hereby incorporated by reference) can be used to *increase the phosphotyrosine content* of EphA2. *Thus*, in another preferred embodiment, this invention relates to the use of *agonists* or antagonists to alter the expression of EphA2 in metastatic cells (specification at page 3, lines 1-8; emphasis added).

The Examiner is requested to note that the EphrinA1-F_c is described in the above passage as only *one example* of an agonist; i.e., a compound that increases the phosphotyrosine content of EphA1.

The link between stimulation of EphA2 activity and an increase in phosphotyrosine content is further described at, for example, page 11, lines 5-10:

> It is believed that B2D6 decreases the growth of metastatic cells. Preliminary results reveal that *B2D6 aggregates EphA2 and blocks about 50% of growth of metastatic breast cancer cells* (which also overexpress EphA2) over the first four hours of incubation. Although EphA2 is not tyrosine phosphorylated in

> metastatic breast cancer cells, *tyrosine phosphorylation is restored [in] these B2D6 treated cells*. Thus, B2D6 is believed to restore normal EphA2 function. (specification at page 11, lines 5-10; emphasis added).

taken together with:

> Moreover, cells that have been transformed to overexpress EphA2 demonstrate malignant growth, and *stimulation of EphA2* is sufficient to *reverse malignant growth* and invasiveness (specification at page 2, lines 10-12; emphasis added)

and further at page 16, lines 8-10:

> *To measure EphA2 stimulation*, the *phosphotyrosine content* of immunoprecipitated EphA2 *was measured* by Western blot analysis with phosphotyrosine specific antibodies (specification at page 16, lines 8-10; emphasis added).

The burden that must be satisfied by the Examiner to support a new matter rejection is a heavy one. Applicants are accorded a *presumption* that the written description is adequate, and the Examiner must provide evidence to rebut this presumption in order to sustain a rejection under 35 U.S.C. §112, first paragraph for lack of written description. Specifically, MPEP 2163.04 states:

> A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption (citations omitted). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the *initial* burden of presenting, by a *preponderance of evidence*, why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims (emphasis added).

The language used in the claims does not need to by synonymous with the terminology used in the original disclosure. MPEP 2163.05. To satisfy the written description requirement, it is necessary only that the newly added claim limitations must be supported in the specification through *express, implicit or inherent disclosure*. The subject matter of the claim need not be

described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. MPEP 2163.02.

According to MPEP 2163.04, in order to establish a *prima facie* case of lack of written description, the Examiner must provide *reasons* why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. The reasons given by the Examiner are conclusory; the Examiner merely states that the specification "does not have support for the claim language 'a compound that increases the phosphorylation content of EphA2'".

It is respectfully that the Examiner has failed do show, by the requisite preponderance of evidence, why a person skilled in the art would not recognize in the Applicants' disclosure a description of the invention defined by the claims. To the contrary, Applicants have shown the claim language used to describe compounds that increase the phosphotyrosine content of EphA2 finds explicit, implicit and inherent support in at least the specification sections described above. Reconsideration and withdrawal of the rejection of claims 58-102 under 35 U.S.C. §112, first paragraph, is accordingly requested.

Summary

It is respectfully submitted that the pending claims 58-103 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
PURDUE RESEARCH FOUNDATION

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

July 27, 2004
Date

By: _____
Victoria A. Sandberg
Reg. No. 41,287
Direct Dial (612) 305-1226

CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service as first class mail, in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 27th day of July, 2004.

By: _____
Name: VICTORIA A. SANDBERG